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BY

J. A. GOODSON AND T. A. HENRY

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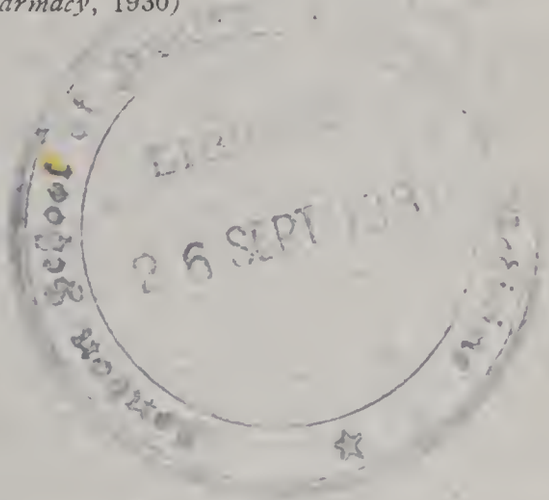

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In January, 1929, the authors received from Dr. H. H. Dale, F.R.S., Director of the National Institute for Medical Research, two samples, A and B, of cinchona febrifuge submitted for examination by the Health Section of the League of Nations. As one of these samples proved on examination to be abnormal in composition, even for such a variable product as cinchona febrifuge, the authors included at a later date a third sample, C, purchased in London.

Although cinchona febrifuge is a well-known material there are comparatively few analyses of it recorded and all that the authors have been able to find are given in Table I.

Analyses 1 and 9 in this Table are not strictly analyses of cinchona febrifuge. The former relates to a product made by double precipitation of the total alkaloids of *Cinchona succirubra* bark and should be called "quinetum." It is of interest to compare this product with that represented by analysis 9 which represents a modern European quinetum, used recently by the Malaria Commission of the League of Nations in clinical trials on malaria. Leaving these two out of account it will be seen that cinchona febrifuge appears to be a very variable product. In this connection analyses 2, 3, 4 and 5 are of particular interest. No. 2 was quoted by MacGilchrist[2] as being the average composition of cinchona febrifuge produced at the Indian Government factory at Mungpoo. No. 3 was given by Gage[3] as representing Indian Government cinchona febrifuge in 1922, and he described it as consisting "of the residual alkaloids remaining after the extraction of quinine from the barks of *C. Ledgeriana* and its hybrid with *C. succirubra*, a certain amount of quinine being added to the mixture to make it approximately similar to the original cinchona febrifuge made from *C. succirubra*," i.e., presumably such a product as is represented by analysis No. 1. Analyses 4 and 5 were made by Howard[4] and represent respectively Indian Government febrifuge tablets examined

in 1913, and febrifuge made at the Government factory in Madras. Considerable variation in composition is indicated by these four analyses and some discussion has taken place regarding the figures for quinidine, owing to the fact that some Indian authorities, who regard cinchona febrifuge as a more effective remedy for malaria than quinine, have suggested that its greater efficacy is due to the large amount of quinidine present. This explanation is, however, no longer tenable since the clinical comparison of quinine and quinidine in malaria, carried out under the auspices of the Medical Research Council, has established quite clearly that quinine is as effective an anti-malarial drug as quinidine[7]. It is noticeable that analyses 2 and 3 both give figures for quinidine which are much higher than those given by Howard in analyses 4 and 5, though even the figure 12·5 given in analysis 4 seems high in comparison with those found by the same author in analyses 6 and 7, which relate to febrifuges of Javanese origin found, on the Indian market[4]. This striking difference in the quinidine content of Indian and Javanese febrifuges is also commented upon by Fletcher[8].

TABLE I.—PUBLISHED ANALYSES OF CINCHONA FEBRIFUGE.

Source of Sample.	No.	Quinine Per cent.	Cinchonidine Per cent.	Quinidine Per cent.	Cinchonine Per cent.	Quinoidine Per cent.	Ash, Moisture Per cent.	Date of Analysis	References.
British India	1	15·5	29·0	—	33·5	17·0	5·0	1891	Dymock, Hooper and Warden[1]
British India	2	7·4	5·8	22·8	18·6	29·1	16·2	1914–5	MacGilchrist[2]
British India	3	10·5	7·0	16·0	23·0	33·0	10·5	1922	Gage[3]
British India	4	2·7	3·4	12·5	12·3	54·9	14·1	1913	Howard[4]
British India	5	8·0	21·0	4·5	21·0	30·0	—	1923	Howard[4]
Java	6	5·8	12·2	8·7	20·0	41·3	3·7	1924	Howard[4]
Java	7	11·9	9·2	4·8	15·3	45·4	—	1922	Howard[4]
European	8	8·5	7·0	8·6	28·3	44·7	4·4	1923	Howard and Chick[5]
European	9	15·0	35·0	5·0	25·0	20·0	—	—	Malaria Commission[6]

The present authors have pointed out elsewhere[9] that apart from variation in composition, due to procedure in different factories or even to variation in processes in the same factory at different times, it is possible that a trustworthy method of analysis for cinchona febrifuge has not yet been developed. It is well known that the separation of two or more organic compounds can rarely be effected with the quantitative precision which is possible in the case of most inorganic substances. Further, the processes available for the

separation and estimation of the four principal cinchona alkaloids have mostly been developed for use with the total alkaloids of "factory bark" in which quinine is the predominant constituent, and Howard and Chick[10], the authors of what is probably the best process for this purpose, point out that when applied to the total alkaloids of other cinchona barks the results are apt to be anomalous. With this warning in mind it was decided that in examining the present samples, each of the fractions "quinine sulphate," "cinchonidine tartrate," "quinidine hydriodide" and "cinchonine," would be carefully investigated in order to ascertain that it was what it purported to be. For the purposes of this secondary examination the present authors have depended upon the fact that Howard and Chick's process gives a reasonably good separation of the two lævorotatory alkaloids, quinine and cinchonidine, from the dextrorotatory pair, quinidine and cinchonine, and that this separation can be checked by determining the optical rotation of the fractions. They have further made use of the fact that the contamination of (*a*) quinine by cinchonidine and vice-versa, or (*b*) of quinidine by cinchonine and vice-versa, can be detected and its amount estimated by methoxyl determinations, since quinine and quinidine each contain one methoxyl group, whilst cinchonidine and cinchonine contain none. It was also found in the course of the work that the presence of amorphous alkaloids ("quinoidine") in cinchonine can be readily detected by the same methods, since "quinoidine" contains methoxyl.

Examination of Samples.

As explained already, only samples A and B received from the League of Nations were examined in the first instance. The results of six separate analyses of these two samples are summarised in Table II.

Febrifuge A was a dark grey powder, containing 3·9 per cent. of moisture and yielding 10·3 per cent. of ash on ignition.

Febrifuge B consisted of a yellowish-grey powder which had cohered into a single friable mass. The moisture content was 7·3 per cent. and the ash left on ignition 4·5 per cent.

Analyses 1 and 2 and the corrected results deduced therefrom in columns 3 and 4 were obtained by the application of Howard and Chick's process to the febrifuges as received. Various difficulties were encountered, due, it was thought, to the large amount of mineral matter in febrifuge A and to the presence of much gummy and tarry material in febrifuge B. It was hoped that these difficulties might be avoided by dissolving each febrifuge in acid, recovering the total alkaloids in the usual way and using the recovered alkaloids for analysis, the results being expressed as percentages of the original products. The process was easier to use

on the recovered alkaloids and the results differed but little from those given by the crude febrifuges. Analyses 5, 6, 7 and 8 were made in this way and corrected results only are given as the primary results were much the same as those recorded in columns 1 and 2 and the corrections were made in the same way.

The following details will serve to indicate the basis on which the corrections were made.

"*Quinine and Cinchonidine.*" Only a small quantity of precipitate came down as quinine sulphate in analysis No. 1, and it was subsequently found that nearly all the quinine was in the "cinchonidine tartrate" precipitate. Consequently in the subsequent analyses 5 and 6, no attempt was made to separate quinine sulphate and both alkaloids were precipitated together as tartrates.

TABLE II.—RESULTS OF ANALYSIS OF FEBRIFUGES A AND B BY HOWARD AND CHICK'S PROCESS.

	Febrifuges as Received.				Total Alkaloids Recovered from Febrifuges.			
	Primary Results.		Corrected Results.		Corrected Results.			
	A per cent.	B per cent.	A per cent.	B per cent.	A per cent.	A per cent.	B per cent.	B per cent.
	1	2	3	4	5	6	7	8
Quinine	1·5	0·9	15·6	nil[x]	17·5	13·9	1·8	nil[x]
Cinchonidine	28·9	0·3	15·1	nil[x]	16·9	18·9	1·5	nil[x]
Quinidine	8·7	6·7	nil	nil	nil	nil	nil	nil
Residual Alkaloids	47·6	77·3	50·3	80·5	46·8	47·4	75·1	73·4
Crude Cinchonine	22·8	36·2	—	—	—	—	—	—
Crystallisable Cinchonine (with correction for solubility)	—	—	15·5	17·5	—	—	—	—
Quinoidine	24·8	41·1	34·8	63·0	—	—	—	—
Ash, moisture	14·2	11·8	14·2	11·8	14·2	14·2	11·8	11·8
Organic impurities (by difference)	nil	3·0	4·8	7·7	4·6	5·6	9·8	14·8

X = In these cases nil means that no crystalline fraction was obtained: there was usually a sticky amorphous deposit, which increased in amount the longer the solution was allowed to stand but from which no crystalline alkaloid could be recovered.

The corrected results in column 3 were obtained from the primary results in column 1 in the following way. The mixed bases recovered from the "cinchonidine tartrate" precipitate, after drying at 120° C. to 125° C. in vacuo contained 5·24 per cent. of methoxyl and had $[\alpha]_D^{25·5}$ – 119·6° for an alcoholic solution (c = 1·63) after decolorisation with charcoal. The methoxyl figure corre-

sponds to 53·74 per cent. of quinine and 46·26 per cent. of cinchonidine in the mixture or to 14·4 per cent. of quinine and 12·4 per cent. of cinchonidine expressed on the original febrifuge. Taking Rabe's[11] figures for the specific rotation, $[\alpha]_D^{15}$ of quinine at $-158°$ and for cinchonidine at $-111°$, such a mixture should have a specific rotation $[\alpha]^D -136°$. The lower value found may be due to the presence of (*a*) hydroquinine $[\alpha]_D^{20} -142°$, (*b*) optically inactive material, or (*c*) possibly small amounts of cinchonine $[\alpha]_D^{17} +229°$, since it is hardly to be expected that an unpurified precipitate of this kind will be entirely free from the components of the precipitation liquors. The difference between the figures found from the methoxyl determination, viz., quinine 14·4 and cinchonidine 12·4, and those given, viz., 15·6 and 15·1 for these constituents in column 3, are due to the inclusion in the latter of the quantities of quinine and cinchonidine found in the "quinine sulphate" and the "quinidine hydriodide" precipitates, which were examined in the same way.

In only one of the analyses of febrifuge B, viz., No. 7, were quinine and cinchonidine found. In this case they were precipitated together as tartrate and the relative quantities of the two alkaloids estimated on the recovered bases from the results of methoxyl determination.

Quinidine. Precipitates which should have been "quinidine hydriodides" were obtained in all six analyses, but on examination these proved to be mainly dirt and saline material, and to contain but little alkaloid. Thus in analysis No. 1 (corrected results in column 3), small amounts of quinine and cinchonidine were precipitated at this stage and were added to the amounts of these alkaloids already found (*see above.*) From none of the hydriodide precipitates from either of the two febrifuges could any recognisable quantity of quinidine be obtained.

Cinchonine. This alkaloid is estimated in this process by precipitating the residual alkaloids, after the removal of any quinine, cinchonidine and quinidine, with alkali and washing the precipitate with ether, or with alcohol of specific gravity 0·94, the assumption being that the amorphous alkaloids are soluble in either solvent and cinchonine insoluble. When the precipitates thus obtained from febrifuges A and B are treated in this way with ether the insoluble residues still contain considerable amounts of amorphous alkaloids, and the separation is no better with alcohol of sp. gr. 0·94. Various methods have been tried in the hope of getting an approximate cinchonine determination, but without success. In analyses 1 and 2, the ether insoluble residue was crystallised from the minimum amount of alcohol and the sum of the crops obtained with the addition of the prescribed correction for the amounts (5·7 and 6·5 per cent. respectively) assumed to be left in the ether, is

given as the amount of crystallisable cinchonine (columns 3 and 4). The crops given by the residue from febrifuge A had m.p. 263° and 262°, $[\alpha]_D + 208°$; those from B had m.p. 262° and 258°. Cinchonine is stated to have m.p. 264° and $[\alpha]_D + 229°$. The figures for cinchonine given in column 3 (febrifuge A) and column 4 (febrifuge B), viz., 15·5 and 17·5 per cent. respectively, represent, therefore, the maximal amounts returnable by this process for the two febrifuges, but these are probably below the true amounts.

In analyses Nos. 5 and 7 cinchonine was not separated. In Nos. 6 and 8 the total residual alkaloidal precipitate was washed with alcohol of sp. gr. 0·94 and the insoluble residues, amounting to 15·9 and 39·8 per cent. respectively, were crystallised from the minimum quantities of boiling alcohol and yielded 12·6 and 7·5 per cent. respectively of cinchonine, expressed on the crude febrifuges: the fractions in the case of febrifuge A had m.p. 263°, 259°, 255°, $[\alpha]_D + 226°$, and in the case of febrifuge B m.p. 264°, 264°, 257°, 253°, $[\alpha]_D + 226°$.

On the basis of all the results given above, the composition of the two febrifuges may be taken to be approximately as follows:—

	A per cent.	B per cent.
Quinine	15·6	1·8
Cinchonidine	16·9	1·5
Quinidine	traces or nil	traces or nil
Residual Alkaloids	48·1	76·3
Crystallisable Cinchonine	12·6	11·0
Crystallisable Cinchonine (with the prescribed correction for solubility)	15·5	17·5
Ash	10·3	4·5
Moisture	3·9	7·3
Organic impurities (by difference) ...	5·2	8·6

Examination of Samples by Chick's Modification of the Howard and Chick Process.

As these two febrifuges were being used by the Malaria Commission of the League of Nations in malaria trials, the authors thought it would be interesting to have them tried in bird malaria, and Dr. J. W. S. Macfie very kindly made the necessary experiments. For this purpose the total alkaloids of febrifuges A and B were made into dihydrochlorides. The preparation from A was found to give a retardation of attack of ten days, whilst that from B gave a retardation of five days, both being given in doses of 5 mgm. The "quinoidines" from both febrifuges were also converted into dihydrochlorides and tried in bird malaria. Both proved to be active, indicating that some active constituent had

escaped precipitation and was now present in considerable concentration in the "quinoidine." It seemed most likely that this active constituent was quinidine. At this juncture there was published by Chick[12] a modified form of that part of the Howard and Chick process which relates to the estimation of quinidine and cinchonine. In this new form, after the separation of quinine and cinchonidine, the total remaining alkaloids are recovered from the precipitation liquors and from this purely alkaloidal product, free from saline material, which in our experience gives so much trouble in the original process, the cinchonine is isolated by making alkaline and shaking out with ether under specified conditions, whilst quinidine is isolated from the ether-soluble alkaloids by converting these into the soluble acetates and precipitating with potassium iodide from a concentrated solution.

A number of analyses were made by this modified process and the "primary" and "corrected" results for a typical analysis of each of the three febrifuges A, B and C is given in Table III.

TABLE III.—Results of Analysis by Chick's Modification of the Howard and Chick Process.

	Primary Results.			Corrected Results.		
	A per cent.	B per cent.	C per cent.	A per cent.	B per cent.	C per cent.
Quinine	1·6	7·2	14·4	14·8	nil	5·5
Cinchonidine	30·4	2·7		13·7	nil	4·7
Quinidine	3·9	4·3	6·0	3·6	3·9	5·4
Total Residual Alkaloids	42·7	64·3	74·9	—	—	—
Crude Cinchonine	18·9	27·2	52·8	—	—	—
Crystallisable Cinchonine	—	—	—	8·2[x]	8·3[x]	34·6
Quinoidine	23·8	37·1	22·1	34·5	55·9	40·3
Ash, moisture, etc.	14·2	11·8	4·6	14·2	11·8	4·6
Organic impurities (by difference)	7·2	9·7	0·1	11·0	20·1	4·9

X = The low values for cinchonine compared with those given in Table II. are explained in the text. They are also in part due to the absence of any correction for solubility.

The corrections required to convert "primary" into "corrected" results for Table III were made on the plan already described in the case of febrifuge C, but certain minor differences in detail were introduced in the case of febrifuges A and B, with a view to getting further information. In the case of A, 34·0 and in the case of B, 28·0 grammes were worked up in batches of 5 to 11 grammes; the corresponding fractions for each batch were mixed and examined as before. The following are details of the results on which the corrections are based.

"*Quinine Sulphate.*"—These fractions from A yielded only 15·5 per cent., expressed on the precipitate, of ether-soluble base having $[\alpha]_D$ −158° (c = 0·54 in alcohol). The quantity was too small for further examination and it was taken as quinine. The fraction from B yielded no quinine. In the case of C quinine and cinchonidine were precipitated together as tartrate (see below).

"*Cinchonidine Tartrate.*"—This fraction from A yielded 78 per cent. of mixed bases, m.p. 155–160° and specific rotation $[\alpha]_D^{20}$ −129·76° (c = 0·892 in alcohol), and which contained methoxyl 4·96 per cent. The methoxyl figure indicates the presence of quinine 52 and cinchonidine 48 per cent. in the mixed bases. These figures are very close to those found previously (p. 242). Such a mixture should have a specific rotation $[\alpha]_D$ −135·4°. From the "cinchonidine tartrate" fraction from B neither quinine nor cinchonidine could be recovered.

The mixed bases recovered from the cinchonidine tartrate of febrifuge C contained methoxyl 5·15 per cent. corresponding to quinine 53·7 and cinchonidine 46·3 per cent. A solution in alcohol after necessary decolorisation with charcoal had $[\alpha]_D^{22}$ − 123·3° (c = 1·798 in alcohol). A mixture of the composition indicated by the methoxyl determination should have $[\alpha]_D$ − 136·2°.

"*Quinidine Hydriodide.*"—These fractions were examined as hydriodides and gave the following results:—

	Melting Point.	Methoxyl Per Cent.	$[\alpha]_D^{20}$ in N-sulphuric Acid.
A	269–270°	6·2	+ 218·8°
B	269–270°	6·2	+ 220·6°
C	269–270°	6·2	+ 218·5°

Quinidine hydriodide melts at 269°, yields methoxyl 6·86 per cent. and has $[\alpha]_D$ + 228·3° (c = 1·54 per cent in N/H_2SO_4). Quinidine base recovered from the A and B fractions had m.p. 168–9°; 168–9° and $[\alpha]_D$ + 246·3° (c = 0·776 in alcohol) and + 249·7° (c = 0·794 in alcohol). Rabe's[12] figures are m.p. 172–3 and $[\alpha]_D$ + 243·5°. It is clear that Chick's process yields practically pure quinidine hydriodide.

"*Cinchonine.*"—The crude cinchonine isolated from the three febrifuges had the following characters:—

	Melting Point.	$[\alpha]_D$	Methoxyl, Per Cent.
A	212°	+101·5°	2·72
B	190°	+116·0°	4·35
C	230°	+182·4°	1·92

The "cinchonines" from A and B were obviously highly impure. Instead of re-crystallising them in one operation from the minimum amount of alcohol, as described on p. 242, they were re-crystallised, one gramme at a time, from alcohol, the mother liquor from each gramme being used for the next, fresh alcohol being added to bring it to the original volume when necessary. The final mother liquor was concentrated until it ceased to yield crystalline crops. The secondary crops thus obtained were re-crystallised once. All crops melting at 253° or higher were taken as "crystallisable cinchonine." The "crude cinchonine" from febrifuge A yielded 43·2 per cent. of this material, m.p. 260–261°, $[\alpha]_D^{20}$ + 229·3° (c = 0·624 in alcohol). That from B gave 30·4 per cent., having m.p. 253–258° $[\alpha]_D^{20}$ + 218·8° (c = 0·612 in alcohol). It was hoped that this method of crystallisation might give higher yields than the customary method previously used (p. 243), but the yields were actually lower and the ordinary method is preferable. Attempts have been made to recover more cinchonine from the mother liquors, e.g., by converting the bases into laevo-tartrates, but, in spite of the fact that cinchonine laevo-tartrate is sparingly soluble in cold water and crystallises well from solutions in boiling water, this method was unsuccessful. An attempt was also made to estimate cinchonine in this "crude cinchonine" by calculating the amount of amorphous alkaloids from a methoxyl determination, but the yield of methoxyl from the amorphous alkaloid proved to be too variable to permit of this.

The crude cinchonine from C was re-crystallised from boiling alcohol by the ordinary process in one lot and yielded 65·6 per cent. of material melting above 256°. The first and last fractions included had m.p. 257° and $[\alpha]_D^{21}$ + 226·6° and m.p. 256° and $[\alpha]_D$ + 229·9°.

On the basis of all the results recorded above the composition of the three febrifuges may be summarised as follows:—

TABLE IV.—Composition of Febrifuges A, B, C.

	A	B	C
Quinine	15·6	1·8	5·5
Cinchonidine	16·9	1·5	4·7
Quinidine	3·9	4·3	5·4
Residual Alkaloids	48·1	76·3	74·9
Crude cinchonine	—	—	52·8
Crystallisable cinchonine	12·6	11·0	34·6
Crystallisable cinchonine (with correction for solubility)	15·5	17·5	36·2
Quinoidine (by difference)	32·6	58·8	38·4
Ash	10·3	4·5	2·8
Moisture...	3·9	7·3	1·8
Organic impurities (by difference)	1·3	4·3	4·9

In compiling the corrected results for Tables II, III and IV no corrections have been made for solubility except in the case of the second figure for crystallisable cinchonine (line 7 of Table IV). Even here the validity of a correction for solubility is doubtful as the solubility of pure cinchonine in alcohol is likely to be less than that of a crude cinchonine in alcohol. Comparing these results with those given in Table I it will be seen that febrifuge A belongs to the same type as No. 3, but is richer in quinine and cinchonidine and poorer in quinidine. B approximates to No. 4 but is much poorer in quinidine. It is of interest in this connection to point out that febrifuge B, and the material represented by analysis No. 4 (Table I) resemble in their low quinine and cinchonidine content a product described by MacGilchrist[13] as "residual alkaloid" and which is stated to have the following average percentage composition : quinine 3 ; cinchonidine 2 ; quinidine 20 ; cinchonine 35 ; quinoidine 30 ; water, etc. 10. They are, however, lower in quinidine and very much lower in cinchonine. "Residual alkaloid" is described by MacGilchrist as prepared by a process similar to that used for cinchona febrifuge but from different trees. C is similar in type to Nos. 6 and 8 and most closely approximates to 8 but is a little poorer in quinine, cinchonidine and quinidine and correspondingly richer in cinchonine.

In making these comparisons it must be borne in mind, in view of the evidence adduced above, that there is no certainty that the various constituents recorded in the analyses in Table I are uniform in quality and it is conceivable *e.g.* that the "cinchonine" returned by one worker may not be the same as the "cinchonine" returned by another. It seems desirable that authors should make a practice by amplifying their analytical statements on this point.

As a result of experience in the examination of these three febrifuges, the present authors are of opinion that the Chick modification of the Howard and Chick process forms a satisfactory basis for the analysis of cinchona febrifuge, provided that it is supplemented by such an examination as is described above of the fractions obtained. The results so obtained for quinine, cinchonidine and quinidine are probably not far from the truth. For cinchonine the results are not yet satisfactory and it seems desirable that the quality of the crude cinchonine obtained should be indicated by the determination of the proportion of crystallisable cinchonine obtainable from it. The only difficulty we have experienced frequently in carrying out the process is that of starting the precipitation of the "cinchonidine tartrate." Sometimes even vigorous agitation of the liquor, scratching of the sides of the vessel, and nucleation with a crystal, of cinchonidine tartrate, will not serve to start precipitation. In such cases the solution should be placed in a flask and evaporated *in vacuo* on a water-bath. Crystallis-

ation usually begins then before the initial volume is reduced to one-half and once it begins is usually complete in a few hours. Further, if the methoxyl method is to be used in determining the relative amounts of quinine and cinchonidine present there does not seem to be any point in attempting an initial separation of quinine as the sulphate. In these three febrifuges the material so separated is mainly dirt and the bulk of the quinine comes down in the second stage as the tartrate.

The authors desire to place on record their thanks to Mr. A. C. Camfield for much assistance in the preparatory and analytical work required in the course of this investigation.

Conclusions.

It is shown that in applying the Howard and Chick process for the separation of the principal cinchona alkaloids to "cinchona febrifuge" the quinine does not as a rule crystallise out as quinine sulphate, but is precipitated at the second stage along with cinchonidine tartrate. The amount of quinine in the bases recovered from the tartrate precipitate can be estimated by the determination of the amount of methoxyl in the mixture and the amount of cinchonidine by difference.

For the estimation of quinidine the Chick modification of the Howard and Chick process is satisfactory, the precipitate consisting of practically pure quinidine hydriodide but the quality of the "cinchonine" isolated by this improved form of the original process is variable. The quality of the "cinchonine" so prepared can be roughly gauged by ascertaining the yield of "crystallisable cinchonine" obtainable from it.

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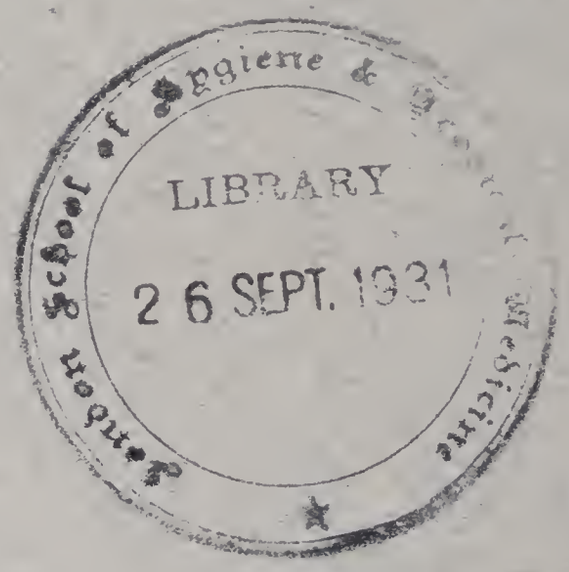
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